11-1-2000

From hopeful monsters to homeotic effects: Richard Goldschmidt's integration of development, evolution, and genetics

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AMER. ZOOL., 40:738–747 (2000)

From Hopeful Monsters to Homeotic Effects: Richard Goldschmidt's Integration of Development, Evolution, and Genetics[1]

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SYNOPSIS. Richard Goldschmidt's research on homeotic mutants from 1940 until his death in 1958 represents one of the first serious efforts to integrate genetics, development, and evolution. Using two different models, Goldschmidt tried to show how different views of genetic structure and gene action could provide a mechanism for rapid speciation. Developmental systems were emphasized in one model and a hierarchy of genetic structures in the other. While Goldschmidt tried to find a balance between development and genetics, critics, such as Sewall Wright, urged him and eventually helped him incorporate population dynamics into his models as well. As such, the history of Goldschmidt's research on homeotic mutants highlights the continuing challenge of producing a balanced and integrated developmental evolutionary genetics.

INTRODUCTION

Recent research on homeotic mutations represents a mixed blessing for Richard Goldschmidt and his place in history. On the one hand, Goldschmidt incorporated homeotic mutations into his research program in the 1940s at roughly the same time that E. B. Lewis also began his research on the homeotic mutant bithorax (Goldschmidt, 1945; Lewis, 1951). As one of the world's leading physiological geneticists, Goldschmidt's research integrated concerns and approaches from developmental, physiological, and evolutionary genetics (Dietrich, 1995). At first glance, his research on homeotic mutations should be of historic and even scientific interest. On the other hand, Goldschmidt's ''heretical'' views denying gradual evolution in favor of sudden speciation and his rejection of the classical gene cast a long shadow. So much so that when Gilbert, Optiz, and Raff recently favorably mentioned Goldschmidt's work on homeotic effects, Howard Lipshitz felt obligated to ''correct'' their ''historical inaccuracies'' (Gilbert *et al.*, 1996; Lipshitz, 1996, p. 616). Unlike Lewis's work, which is held up as setting the ''paradigm for linking genetic analysis, developmental biology, and evolution,'' Lipshitz argues that ''Goldschmidt contributed little insight into the genetic or developmental basis of the ''homeotic'' transformations he described and was at best confused about their evolutionary implications'' (Lipshitz, 1996, p. 616).

Goldschmidt often presented his views in a way that he knew would invite controversy. It is not my intention to defend his views, but to present a careful analysis of the history and logic of his research in evolutionary developmental genetics. Regardless of contemporary assessments, Goldschmidt's efforts from 1940 until his death in 1958 stand out as one of the first attempts to develop a theory which integrated models of genetic structure, genetic action, developmental processes, and evolutionary dynamics. In his 1940 book, *The Material Basis of Evolution*, Goldschmidt presented his theory by developing one model, which included the classical gene, and one model which did not. Using the classical gene, Goldschmidt argued that new species might originate as hopeful monsters from mutations in developmentally significant loci (developmental macromutations). Building an analogy as Darwin had between artificial and natural selection, Goldschmidt argued that if a single developmental macromutation could have a large effect, then a model

[1] From the Symposium *Evolutionary Developmental Biology: Paradigms, Problems, and Prospects* presented at the Annual Meeting of the Society for Integrative and Comparative Biology, 4–8 January 2000, at Atlanta, Georgia.

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of genetic change based on chromosomal rearrangements of different sizes could produce even larger changes. More specifically, a systemic rearrangement of a chromosome, which Goldschmidt called a systemic mutation, could quickly produce a new developmental system and potentially a new species. Of these two mechanisms, systemic mutations emphasized the importance of large-scale changes in genetic structure (chromosomal rearrangements). After 1940, Goldschmidt sought to bolster his model of mutation as chromosomal rearrangement with further research on genetic structures, eventually resulting in a genetic hierarchy of structural units ranging from chromomeres detected within salivary gland chromosome bands up to blocks of euchromatin first described by Heitz (Dietrich, 2000, p. 103). Goldschmidt's second mechanism of evolutionary change via developmental macromutations emphasized developmental and evolutionary processes instead of genetic structure. After 1940, Goldschmidt's research on homeotic mutants in *Drosophila* was intended to demonstrate that developmental macromutations could play a role in evolution.

While he was never able to meet his critics' objections regarding chromosomal rearrangement, his advocacy of a significant evolutionary role for macromutations effecting developmental processes was more positively received. In response to his critics, Goldschmidt continued to refine his views until the end of his life. In fact, after 1940, Goldschmidt attempted to refine and clarify his evolutionary views by entering into a dialogue with Sewall Wright about the evolutionary significance of homeotic mutations and the population dynamics necessary for major mutations to play a role in evolution. In doing so, Goldschmidt recognized and tried to address the problem of integration that remains a challenge for evolutionary developmental genetics today.

SYSTEMIC MUTATIONS AND HOPEFUL MONSTERS

When Goldschmidt wrote *The Material Basis of Evolution* in 1940 he was 62 yr old. Four years earlier, he had been forced by the Nazis to leave his prestigious position as a director in the Kaiser Wilhelm Institute for Biology in Berlin-Dahlem. In Germany, Goldschmidt had also been an editor of a leading journal, author of several widely used genetics textbooks, and a leading authority on issues of sex determination, geographic variation, genetics, and zoology. The strength of his reputation in Germany and the United States allowed him to find a position at the University of California, Berkeley where he started a new life that quickly became enmeshed in two major controversies (Dietrich, 1996). Based on evidence concerning the prevalence of position effects and chromosomal rearrangements, Goldschmidt actively argued against T. H. Morgan's model of the gene as a bead-on-a-string. Morgan's classical model of the gene posited that it was simultaneously a unit of structure, function, mutation, and recombination (Allen, 1974; Carlson, 1966; Gilbert, 1988; Dietrich, 2000). In place of the classical gene, Goldschmidt advocated a hierarchy of genetic units. Instead of considering mutations to be changes in the chemical constitution of a classical gene, he argued that all genetic changes were in fact rearrangements of different sizes and effects. Viewing genetic changes as rearrangements underwrote Goldschmidt's equally controversial view of macroevolution by systemic mutation; in fact, he characterized his evolutionary views as the phylogenetic consequences of his views on the gene.

In *The Material Basis of Evolution*, Goldschmidt presents two different genetic mechanisms to explain the production of new species. Neither of them was the Neo-Darwinian mechanism of the gradual accumulation of small mutations. Goldschmidt argued that evolution above and below the species level was governed by different processes. Put another way, microevolution was not sufficient to cross the "bridgeless gap" separating species. These bridgeless gaps between species could only be spanned by macromutations—either systemic mutations or mutations with large effects in developmental systems.

Systemic mutations are large changes of the primary pattern of the chromosome (the reaction system of the chromosome) resulting in a new, well integrated pattern. In Goldschmidt's words, ''A complete repatterning might produce a new chemical system which as such, *i.e.*, as a unit, has a definite and completely divergent action upon development, an action which can be conceived as surpassing the combined actions of numerous individual changes by establishing a new chemical system'' (Goldschmidt, 1940, p. 203). For Goldschmidt, the linear arrangement of the genetic material had a significant impact on the system of reactions produced. Like most geneticists at the time, Goldschmidt thought that genes were made up of proteins. These proteins acted as substrates or catalysts for a network on system of reactions. A new linear order in the genetic material would alter the availability of proteins for different localized reactions thereby producing a new system of reactions. Goldschmidt allowed that new genotypic patterns could emerge in a series of consecutive steps. These changes in chromosome pattern may not have any phenotypic effect until a new stable genotypic and phenotypic pattern was created, giving the impression of a sudden origin for a new phenotype. Systemic mutations appeared sudden, but not because the genetic mechanism producing them was rapid.

Goldschmidt's argument for systemic mutations was firmly grounded in his theory of physiological genetics. Based on twenty-five years of research on the genetic basis of sex determination in the Gypsy moth, *Lymantria dispar*, Goldschmidt had developed a theory of gene action in terms of the ability of genes to produce different amounts of substance at different rates. Using different varieties of gypsy moth, Goldschmidt discovered in 1911 that he could produce a series of intermediate froms ranging from male to female. In order to explain the complete series of intergradations, Goldschmidt argued that the male and female factors in each individual had different strengths or valences that were balanced against each other (Richmond, 1986, pp. 137–233). So, which sexual phenotype appeared depended on the quantitative relation between the strength of the factors. Each factor did not produce a unitary trait; it produced some substance (an enzyme or hormone perhaps) in some quantity. Because quantity and rate of production could vary, the potency or valence of the factor was said to vary, to lie in a range from strong to weak. According to Goldschmidt a normal female contained two female factors or alleles (FF) and was heterozygous for the male factors (Mm). Females were thus designated FFMm, while males were designated FFMM. If both factors in the MM pair were weak and both FF were strong, the female would predominate over the male and produce an intersex or even possibly a male which appeared completely female. Because the production of male and female moths depended on the balance of male and female factors, Goldschmidt named his theory, the balance theory of sex.

In his efforts to understand the mechanism for intersexual development after 1917, Goldschmidt began to chart the development of different distinguishing sexual characteristics. What he found was that even though all of the body's cells had the same genetic components and so the same genetic basis for sex characteristics, adult intersexual organisms frequently appeared as mosaics of different sexual characteristics, some male, some female, some intermediate. To explain why intersexual organisms were not uniform in their expression of intersexual characteristics, Goldschmidt proposed what he called the Time Law of Intersexuality. In his words, ''An intersex is an individual which has developed as a male (or female) up to a certain time point; from this turning point the development has continued as a female (or male). The increasing degree of intersexuality is an expression of the recession of the turning point, that is, its occurrence at an earlier stage in development. And lastly, the condition of any particular organ is determined by the time of its differentiation—whether it is before or later than the turning point'' (Goldschmidt, 1923, p. 91). Different organs could, thus, express different sexual or intersexual characteristics.

In his physiological genetics, Goldschmidt generalized his findings from sex determination in *Lymantria* in order to explain phenomena such as penetrance. Normal expression of a trait, according to

Goldschmidt, depended on the corresponding gene's ability to produce enough substance at the right rate during critical periods of development (Goldschmidt, 1938, p. 65). If not enough substance was produced, then the threshold for expression would not be crossed. The phenotype for a systemic mutation would appear suddenly because its expression depended on a threshold effect. In Goldschmidt's words, a systemic mutation is recognized ''only when by chance a pattern, viable in homozygous condition and above the threshold, has been reached; *i.e.*, such as the patterns actually found when comparing species, does the new system of reaction suddenly emerge, though prepared by subliminal steps'' (Goldschmidt, 1940, p. 246). Systemic mutations produce new species in what appear to be large and rather sudden steps, actually they are large-scale chromosomal changes which may have been developing for quite some time.

A key part of Goldschmidt's case for systemic mutations rests on the possibility of a quick change from one stable developmental system to another. In the last third of *The Material Basis of Evolution,* Goldschmidt was concerned to demonstrate that a single genetic change could alter a functioning developmental reaction system into a fundamentally different but still functional developmental reaction system. Goldschmidt deliberately pointed out that this part of his argument does not depend on his rejection of the classical model of the gene. The developmental macromutations he discussed in this last section could be understood as mutations in genes or as systemic mutations. Demonstrating that changes in developmental regulation could produce large phenotypic effects, according to Goldschmidt, made systemic mutations a more plausible means for producing a new species (Goldschmidt, 1940, pp. 251–252). It is important to note that Goldschmidt thought that these developmental macromutations produced what he called hopeful monsters. These hopeful monsters were not the result of systemic mutations and, as we shall see, not everyone wanted to associate them with the production of a new species.

The developmental macromutations discussed at the end of *The Material Basis of Evolution* captured the central idea of Goldschmidt's thought on evolution in 1940; namely, that ''a single mutational step affecting the right process at the right moment can accomplish everything, providing that it is able to set in motion the ever present potentialities of embryonic regulation'' (Goldschmidt, 1940, p. 297). This idea of developmentally significant mutations with large effects garnered a significant amount of support. Biologists, such as Curt Stern, W. Dwight Davis, G. G. Simpson, and Sewall Wright recognized the importance of developmental macromutations. Indeed this idea continued to have the support of biologists after the advent of molecular genetics (Wilson, *et al*., 1974; King and Wilson, 1975; Sarich, 1980; Gould, 1982). This support did not extend, however, to Goldschmidt's theory of systemic mutations (Dietrich, 1992, 1995). In general, Goldschmidt's theory of speciation via systemic mutation had no support among evolutionary biologists. On the one hand, its emphasis on chromosome structure rooted key mechanisms of evolutionary change within an unresolved controversy concerning the nature of the gene. On the other, by placing so much importance on genetic structure, it neglected the roles played by developmental processes and evolutionary dynamics (Wright, 1941).

Homeotic mutations

After the publication of *The Material Basis of Evolution,* Goldschmidt sought to further support his views with research on homeotic mutants in *Drosophila melanogaster*. The term ''homeosis'' had been coined by William Bateson in 1894 to describe dramatic variations in which ''something has been changed into something else'' (see Lewis, 1994). Later, Dobzhansky described homeosis as ''a very interesting class of mutations [which] causes transformation of some organs into others, revealing the homology between the two'' (Dobzhansky, 1937, p. 18). Goldschmidt focused his research on the homeotic mutants podoptera, ''transformation of wings into leglike structures,'' and tetraltera, ''transformation of wings into halteres,'' in *Drosophila melan-*

ogaster (Goldschmidt *et al*., 1951). This research on homeosis was intended to support both his view of genetic structure and his view of evolution.

After Goldschmidt rejected the classical model of the gene, he sought to develop an alternative understanding of genetic structure in terms of a hierarchy of structural and functional units. Beginning in 1944, he articulated a hierarchy which extended from barely visible structures, such as chromomeres, to large segments of the chromosome, such as heterochromatic blocks (Dietrich, 2000). The genetic regions producing homeotic effects were considered to be fairly large structures because in *Drosophila* there was a ''concentration'' of homeotic mutants in a region of the third chromosome; *i.e*., ''polycomb *ca*. 45.0, proboscipedia 47.7, tetraptera 51.3, aristopedia 48.5, bithorax 58.8, ss-supressor 63.7, pointed wing 94.1'' (Goldschmidt, 1958, p. 182). All of these mutants affected the determination of segmental appendages, which led Goldschmidt to interpret this segment of the third chromosome as a field ''vitally concerned with the processes of segmental determination'' (Goldschmidt, 1958, p. 182). Because he understood these homeotic mutants to alter the development of the imaginal discs, Goldschmidt claimed that ''the whole intact section [of the chromosome] controls certain parts of the process of normal development of the discs'' (Goldschmidt, 1958, p. 182). This interpretation allowed Goldschmidt to associate large chromosomal regions with developmental functions and fields.

Within this scheme, hereditary units were not units of mutation, they were the units necessary for the process of normal development (Goldschmidt, 1944, p. 197). Goldschmidt recognized that mutations often produced specific, localizable effects. He argued that it was a mistake to limit the location of a gene responsible for the normal or wild-type function to the small area altered by a point mutation. The production of a normal function could be the result of structures spread over a much larger region of the chromosome. In the case of H. J. Muller's study of scute mutants, many different mutants spread over an 8–10 band region had an altered the scute phenotype. Goldschmidt argued that locating the scute gene at the location of any one mutation mischaracterized what was genetically necessary to produce the phenotype in question. The clustering of homeotic mutants allowed Goldschmidt to argue that normal development of segmental appendages was best understood in terms of a large chromosomal region and its associated functional field, rather than in terms of classical genes which combined structure, function, mutation, and recombination into one small and indivisible unit.

Even though Goldschmidt argued that mutants were not a guide to the genetic structures associated with normal genetic functions, he did think that experimentation on homeotic mutants could shed light on problems of genetic action and evolution. In particular, he deliberately chose to work on the homeotic mutants podoptera and tetraltera because they had variable penetrance. Goldschmidt knew that the low penetrance of podoptera and tetraltera would make genetic analysis difficult, but it also made them more interesting in terms of the analysis of genetic action and its evolutionary consequences. Drawing on his theory of physiological genetics, Goldschmidt developed what he called a phenogenetic analysis of homeosis, an analysis of the action of homeotic mutations upon development (Goldschmidt, 1938, p. 23).

In his *Tempo and Mode of Evolution* (1944) G. G. Simpson had raised a number of objections to Goldschmidt's ''evolutionary generalizations'' concerning homeotic mutants. Simpson argued that homeotic mutants were not different in kind from any other form of mutation: homeotic mutations may have large effects, but they do not create new species. In addition, Simpson argued that ''the appearance of a mutant individual is not evolution'' (Simpson, 1944, p. 53). The evolution of homeotic mutants, according to Simpson, still depended on selection acting on populations of individuals. In his own review of Goldschmidt's views in 1941, Sewall Wright had made the same criticism. In his words, ''Goldschmidt gives no serious discussion of questions of dynamics . . . . Yet the dynamics of the pos-

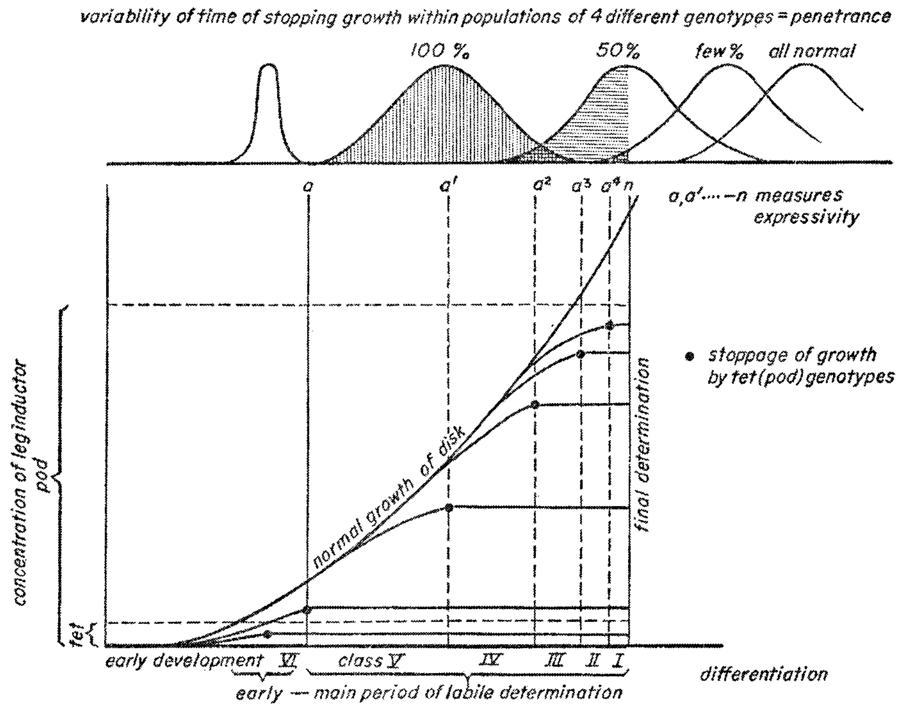

FIG. 1. Diagrammatic representation of phenogenetic explanation of the podoptera effect. See text for explanation of figure. Reprinted from Goldschmidt, 1951, p. 162.

tulated accumulation of subliminal steps in chromosome repatterning and of the establishment of the systemic mutations, once the threshold has been passed, are questions which must be considered'' (Wright, 1941, p. 166).

In 1946, Goldschmidt responded to Simpson's criticism with a phenogenetic analysis which focused on how to explain the high variability of homeotic mutations. Simpson had suggested that the variability could be explained in terms of the selection of many, small modifiers. Goldschmidt thought that Simpson was in danger of ''forgetting that evolution is to a large extent also a problem of development'' and argued that a single mutant could express all of the variability described by Simpson (Goldschmidt, 1946, p. 312).[3]

[3] As he tended to do, Goldschmidt's argument against Simpson is stated too strongly. In his phenogenetic analysis he recognizes the influence of other genes and does not ascribe all phenotypic variability to variability in the developmental expression of a single mutant. See below.

In order to make his case, Goldschmidt argued that threshold effects, reaction rates, and developmental timing could explain the low penetrance, high variability, and asymmetry of actual homeotic mutants, such as podoptera. Where Simpson had to invoke a complex set of modifiers, Goldschmidt invoked a single, flexibile developmental system based on a homeotic mutant.

In their monograph on the podptera effect (1951), Goldschmidt, Aloha Hannah, and Leonie Piternick represent the phenogenetic explanation for the podoptera effect graphically (see Fig. 1). First, the podoptera effect was described as ranging from one of the wings being spread out at a right angle to the body (class I) to wings with notches and blisters (class II) to much shortened wings but with some wing morphology still apparent (class III) to a even shorter wing divided into the costal cell, two pieces of wing blade and the allula (class IV) to the complete separation of the costal cell and its transformation into a leg-like structure (class V) to a set of four irregular knobs (class VI) (Goldschmidt *et al.*, 1951, p. 82). Goldschmidt explained these phenotypic differences in terms of differences in the concentration of leg inducer at different periods of development. These different phenotypes represented different points at which growth was stopped when determination became irreversible shortly after pupation. Goldschmidt represented this situation by plotting differential growth during the period of labile determination against the concentration of leg inducing substance. Under normal conditions, the wing disk continues to grow during the labile period and crosses a threshold for normal expression (horizontal dashed line) before determination becomes irreversible (represented by the vertical line n). With podoptera and tetraltera, normal growth of the wing disk is stopped, but the different classes of mutant phenotypes are explained in terms of the point at which the wing disk stopped growing. Moreover, individual differences in expressivity were explained in terms of variation in those stopping points. Different stopping points between a^1 and a^2 explained differences of expressivity with class IV podoptera mutants, for instance.

The same growth curve was used to explain the penetrance of the podoptera effect. Goldschmidt explained penetrance (percentage of individuals in a population producing a given phenotype) by appealing to the concepts of genetic potency and thresholds that he had developed to explain sex determination in *Lymantria* (Goldschmidt, 1958, p. 380). The podoptera effect was produced when the loci producing the inducing substance were not strong enough, *i.e.*, they did not produce enough substance during the period of labile determination. Low penetrance was the result of genetic and environmental variation which effected the amounts of inducers produced, the rates of growth and the position of the threshold for normal expression.

Goldschmidt's phenogenetic explanations of homeotic effects like podoptera and tetraltera were a means of integrating genetics and development. However, Simpson's and Wright's challenge of addressing the evolutionary dynamics of that would allow a homeotic mutation to spread through a population remained. In the 1940s, Sewall Wright and Richard Goldschmidt worked out a means for explaining how a homeotic mutations might spread by taking advantage of their low penetrance to incorporate them into Wright's shifting balance theory of evolution.

Goldschmidt and Wright had known each other since Wright's student days when Goldschmidt was stranded in the U.S. for the duration of the First World War. As the world's leading physiological geneticists, they were very familiar with each other's work and were well aware of the difficulties of understanding gene action. In 1944, Wright spent a year at Berkeley, just as Goldschmidt was developing his experimental program on podoptera. Wright and Goldschmidt were known to be on good terms and undoubtedly talked shop often (Wright, 1976).

As Goldschmidt began publishing his work on podoptera, he suggested that the low penetrance of this homeotic mutant would allow it to persist in a population and accumulate those subliminal changes necessary to produce a macroevolutionary change (Goldschmidt, 1946). After he sent a set of reprints to Wright in 1949, Wright offered a more sophisticated model for the evolutionary dynamics of a homeotic mutation. In his letter to Goldschmidt, Wright wrote:

> It seems to me that a finely divided population structure, at least in some localities within a species, is even more important in the establishment of a mutation with major effects such as your homeotic mutations than in the case of ones with minor effects on ordinary quantitative variation. Such a mutation is exceedingly unlikely, it seems to me, to appear in a form that has any chance of establishment as long as it is a segregant in a large random breeding population, since it cannot acquire the modifiers necessary to smooth it out in such a genetic environment. With a finely divided population structure, with some exchange of genes between localities but not much, each locality will acquire a different set of gene frequencies of modifiers as a result of

> chains of historic accidents of which the accumulation of sampling deviations in only one example. A homeotic gene, capable of being carried at low frequency throughout the species because of low penetrance . . . may thus be tried out in all localities with a reasonable chance of encountering a genetic and environmental milieu in which it is superior to type and in which there is sufficient isolation to permit crystalization about a new species type (Wright, 1949).

Goldschmidt was naturally pleased and responded to Wright saying, ''if you say that a finely divided population structure is the proper setting I am certainly glad to hear about it'' (Goldschmidt, 1949). The next year Wright incorporated major mutations, such as homeotic mutations, into an explanation of his shifting balance theory. Where populations are finely divided, Wright argued that, homeotic mutants can be protected by low penetrance and so carried at ''low frequencies as a part of the field of potential variability which may ultimately be used'' (Wright, 1950, p. 279). Wright was careful to note, however, that evolution is not driven by mutation or limited by lack of adaptive mutants when a new ecological opportunity arises. Moreover, Wright insisted that a major mutation became more advantageous in combination with other modifying loci (see Fig. 2). The success of a major mutant depended crucially on finding the right set of genetic modifiers and the right ecological opportunity (Wright, 1977).

Although Goldschmidt eagerly acknowledged Wright's support, several important differences remained between them. Wright continued to emphasize that the spread of a major mutation was distinct from a mutation which produced reproductive isolation. Wright basically claims that Goldschmidt confuses mutations of large effect with mutations which produce isolation. A major mutation need not be macroevolutionary and an isolating mutations need not have a large phenotypic effect (Wright, 1949). Homeotic mutations could produce large and important evolutionary effects, but they were not necessarily the key to speciation.

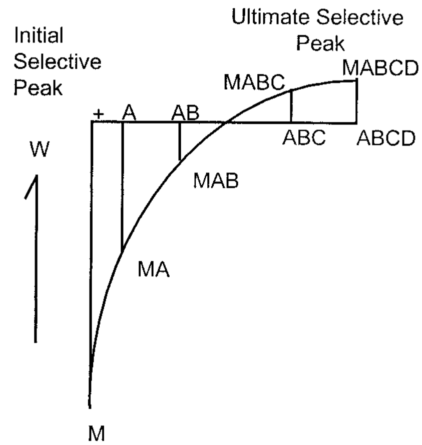

FIG. 2. Wright's model for the fixation of a major mutation. An initially deleterious mutation, M, with modifiers, A, B, C, D. Combinations MABC and MABCD are superior to any combination without the mutant. Redrawn from Wright 1977, figure 13.9.

Goldschmidt with his characteristic lack of restraint was much more willing to generalize and to argue that the evolution of homeotic mutants was evidence for the possibility of macromutations and systemic mutations (Goldschmidt, 1958). However, to his credit Goldschmidt, incorporated Wright's suggestions and advocated an important role for population structure and natural selection in the spread of major mutations (Goldschmidt, 1952*a*, pp. 101–103). Where Wright tended to emphasize population structure and the elements of his shifting balance theory, Goldschmidt emphasized developmental processes. According to Goldschmidt, regulatory and integrative processes of development relieved ''the evolutionary processes, in the case of macromutations, of a good deal of the work which would be necessary if everything were based upon more and more modifiers for a thousand details.'' For this reason he tried to ''convince evolutionists that evolution is not only a statistical genetical problem but also one of the developmental potentialities of the organism'' (Goldschmidt *et al*., 1951, p. 103).

CONCLUSION

Richard Goldschmidt's research on podoptera has not become the paradigm for research on homeotic genes. He knew that it wouldn't. ''Classical genetics,'' he wrote, ''was mainly interested in mutants with perfect penetrance [such as bithorax] . . . and expressivity (easily classified phenotype) as these lent themselves to crossing-over and localization experiments'' (Goldschmidt, 1953, p. 108). Goldschmidt was not concerned with traditional genetic analysis. He wanted to articulate a genetics that integrated developmental and evolutionary processes. His phenogenetic analysis of these ''intractable mutants'' was meant to address issues of gene action, evolutionary dynamics, and their interactions. Richard Goldschmidt's research on homeotic mutants is not significant because it was right or paradigmatic. It is significant because it represents one of the first serious efforts to integrate genetics, development, and evolution. As such, Goldschmidt's research reveals the great difficulty of balancing the different contributors to a developmental evolutionary genetics. Consider the major flaws with his different models of macroevolution. Evolution by systemic mutations placed too much emphasis on a model of genetic structure which could not be confirmed or fully integrated with a model of gene action (not every inversion or chromosomal repatterning produces a phenotypic effect). Evolution by developmental macromutations placed too much faith in the ability of developmental processes to create functioning new species from major genetic changes. Goldschmidt needed Wright's counsel to provide a reasonable evolutionary dynamics for major mutations, which in turn made speciation by macromutation a possibility. Yet even then Goldschmidt noted the tendency to drop developmental considerations in favor of population genetics. Then as now, creating an integrated and balanced evolutionary developmental genetics was the challenge facing research on homeotic effects.

ACKNOWLEDGMENTS

I am grateful for comments provided by the anonymous referees for this journal and the audience at the Symposium on Evolutionary Developmental Biology. Research for this paper was supported by a grant from the National Science Foundation (SBER 94-12384).

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